INTRODUCTION: Low grade gliomas lack neovascularization when compared to their high grade counterparts. Bone marrow-derived cells (BMDCs) are recruited to the tumor site and mediate the angiogenic switch during malignant transformation. This process ultimately supports the exponential growth kinetics displayed by high grade tumors that often exhibit aberrant vasculature. In order to elucidate the functional consequence of impairing BMDCs, in particular myeloid-derived suppressor cells (MDSC), we employed JAK 1/2 inhibitors. JAK 1/2 inhibition prior to the angiogenic switch in low grade glial tumors resulted in reduced neo-vascularization (CD31) and cellular proliferation (Ki67+). To conclusively prove impaired MDSC recruitment, we pursued a series of bone marrow transplant studies to demonstrate the effect of interrogated JAK 1/2 signaling on GFP+ BMDCs recruitment to the tumor core and periphery.

METHODS: A spontaneous, transgenic PDGF-driven murine glioma model was utilized to recapitulate low-grade to high-grade progression. Tumor bearing animals were lethally irradiated (10Gy) at 2 weeks old and transplanted with age appropriate bone marrow from GFP donor mice. After a 4 week bone marrow reconstruction, the animals were treated with JAK1/2 inhibitors via oral gavage for 4 weeks. Immunofluorescence was used to characterize the impact on GFP+ BMDC recruitment at the tumor site. Flow cytometry was then used to quantify GFP+ BMDCs at the tumor site and periphery (blood and bone marrow).

RESULTS: The number of GFP+ BMDCs recruited to the tumor core is markedly reduced in post-transplant JAK treated animals. These animals demonstrate a significant survival advantage and exhibit delayed transformation on MRI and histologically, consistent with our previous findings. Flow cytometry and immunofluorescence demonstrates impaired Cd11b+/Gr1+ mobilization in the bone marrow, peripheral blood and at the tumor core.

CONCLUSION: The utility of GFP+ bone marrow transplant model system proves that JAK 1/2 Inhibition plays a direct role in impairment of MDSC infiltration.